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SYNERGISM BETWEEN LEUKOTRIENE B4 AND THROMBOXANE A2 IN MEDIATING ACID ASPIRATION INJURY

BY

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Acid aspiration leads to thromboxane (Tx) dependent lung neutrophil (PMN) sequestration associated with microvascular permeability increase. Leukotriene (LT) B4 is postulated to be a co-factor in the Tx-induced inflammatory response. This study tests the interaction between LTB4 and Tx focusing on LTB4 induction of PMN sequestration following acid aspiration. Anesthetized rats underwent tracheostomy and insertion of a cannula into a left lung segment. This was followed by

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instillation of either 0.1 ml 0.1N HCl (n=18) or 0.1 ml saline in control rats (n=18). When assayed at three hours acid aspiration led to increased plasma levels of LTB4 and TxB2, higher than control values ($p < 0.05$). The rise in plasma LTB4 was correlated ($p < 0.05$, $r=0.83$) with sequestration of neutrophils in the non-aspirated lung. There were 95 PMN/10 high power fields (HPF) in the aspirated and 45 PMN/10 HPF in the non-aspirated side, higher than control values of 8 PMN/10 HPF and 5 PMN/10 HPF (both $p < 0.05$). The entrapment of PMN was associated with an increase in protein concentration in bronchoalveolar lavage (BAL) of the aspirated and non-aspirated sides 4520 ug/ml and 2320 ug/ml respectively relative to saline aspirated control rats 480 ug/ml and 410 ug/ml (both $p < 0.05$). There was an increase in lung wet to dry weight ratio (W/d) of 6.5 and 5.3, higher than control values of 3.4 and 3.3 (both $p < 0.05$). Pretreatment of other rats (n=18) with the lipoxygenase inhibitor diethylcarbamazine (DEC) IV 90 mg/kg as a bolus followed by 40 mg/kg/h prevented aspiration induced rise in plasma LTB4 and TxB2. Further, there was an attenuation of: lung leukosequestration (56 and 28 PMN/10 HPF); protein leak in BAL (2120 ug/ml, 1240 ug/ml) and lung edema (5.0,3.6)(all $p <$ 0.05). Pretreatment of other rats (n=12) with the LT receptor antagonist FPL 55712 IV 80 ug/kg as a bolus followed by 40 ug/kg/h did not prevent the aspiration induced rise in LTB4 or TxB2, but otherwise was as effective as DEC in preventing injury. Finally, other HCl-aspirated rats (n=8) were pretreated intravenously with the Tx synthetase inhibitor OKY 046 or the Tx receptor antagonist SQ 29548. Both agents limited the aspiration induced rise in plasma LTB4 ($p < 0.05$). The data indicate that localized acid aspiration induces synthesis of LTB4 and TxA2. Inhibition of either LT or Tx will limit PMN adhesion and increased lung permeability.

ABSTRACT

Acid aspiration leads to thromboxane (Tx) dependent lung neutrophil (PMN) sequestration associated with microvascular permeability increase. Leukotriene (LT) B_4 is postulated to be a co-factor in the Tx-induced inflammatory response. This study tests the interaction between LTB_4 and Tx focusing on LTB_4 induction of PMN sequestration following acid aspiration. Anesthetized rats underwent tracheostomy and insertion of a cannula into a left lung segment. This was followed by instillation of either 0.1ml 0.1N HCl (n=18) or 0.1ml saline in control rats (n=18). When assayed at three hours acid aspiration led to increased plasma levels of LTB_4 and TxB_2, higher than control values ($p < 0.05$). The rise in plasma LTB_4 was correlated ($p < 0.05$, r=0.83) with sequestration of neutrophils in the non-aspirated lung. There were 95 PMN/ 10 high power fields (HPF) in the aspirated and 45 PMN/10HPF in the non-aspirated side, higher than control values of 8 PMN/10HPF and 5 PMN/10HPF (both $p < 0.05$). The entrapment of PMN was associated with an increase in protein concentration in bronchoalveolar lavage (BAL) of the aspirated and non-aspirated sides 4520 μg/ml and 2320 μg/ml respectively relative to saline aspirated control rats 480 μg/ml and 410 μg/ml (both $p < 0.05$). There was an increase in lung wet to dry weight ratio (W/d) of 6.5 and 5.3, higher than control values of 3.4 and 3.3 (both $p < 0.05$). Pretreatment of other rats (n=18) with the lipoxygenase inhibitor diethylcarbamazine (DEC) IV 90 mg/kg as a bolus followed by 40 mg/kg/h prevented aspiration induced rise in plasma LTB_4 and TxB_2. Further, there was an attenuation of: lung leukosequestration (56 and 28 PMN/10HPF); protein leak in BAL (2120 μg/ml,1240 μg/ml) and lung edema (5.0, 3.6)(all $p < 0.05$). Pretreatment of other rats (n=12) with the LT receptor antagonist FPL 55712 IV 80 μg/kg as a bolus followed by 40 μg/kg/h did not prevent the aspiration induced rise in LTB_4 or TxB_2, but otherwise was as effective as DEC in preventing injury. Finally, other HCl-aspirated rats (n=8) were pretreated intravenously with the Tx synthetase inhibitor OKY 046 or the Tx

receptor antagonist SQ 29548. Both agents limited the aspiration induced rise in plasma LTB_4 ($p < 0.05$). The data indicate that localized acid aspiration induces synthesis of LTB_4 and TxA_2. Inhibition of either LT or Tx will limit PMN adhesion and increased lung permeability.

INTRODUCTION

Acid aspiration induced lung leukosequestration and edema are dependent upon thromboxane (Tx)A_2. Thus, inhibition of Tx synthesis prevents neutrophil sequestration and the increase in microvascular permeability (1). However, the mechanism by which Tx leads to PMN-endothelial adhesion, a prerequisite for injury is not clear. In one study, infusion of a large dose of the Tx mimic, U 46619 into pigs led to lung leukosequestration (2). Further, an in vitro study with U 46619 induced neutrophil adhesion to an endothelial monolayer which was dependent upon activation of a neutrophil adhesion receptor, the CD 18 complex (3). These data are consistent with Tx functioning as a chemoactivator of neutrophils. Surprisingly, however the Tx adhesion process could be inhibited with a leukotriene (LT) receptor antagonist (3).

We hypothesize that endogenous TxA_2 may exert its effect on PMN adhesion via a synergistic interaction with another intermediary, LTB_4. This postulate is based on the observation that in another setting, that of ischemia we have shown cross reactivity between cyclooxygenase and lipoxygenase pathways. In addition, inhibition of either LTB_4 or Tx has been found to limit lung leukosequestration and reduce the subsequent protein leak following hindlimb ischemia (4,5). The fact that both eicosanoids may be required to induce PMN-endothelial interactions has been shown in another setting. Thus, authentic LTB_4 placed in a dermabrasion chamber induces diapedesis. This was reduced by inhibition of Tx synthesis (6). The corollary was also true where Tx mimic induced neutrophil accumulations were prevented with lipoxygenase inhibition (unpublished data). Since TxA_2 may induce LTB_4 synthesis and visa versa and both are capable of enhancing PMN adhesion via CD 18 expression (7), we hypothesized that in the setting of aspiration, either eicosanoid may initiate the process of neutrophil activation to increase their adhesiveness to the pulmonary microvasculature but that both are necessary for adhesion to be completed.

The current study tests whether localized acid aspiration leads to LTB_4 generation, lung leukosequestration and generalized permeability edema. Further, it evaluates the dependence of these events on TxA_2 synthesis. The results show that Tx synthesized in response to acid aspiration leads to LTB_4 generation. Inhibition of either eicosanoid is effective in limiting neutrophil sequestration and permeability increase in non-aspirated lung segments indicating that both eicosanoids are obligate co-factors in the process of PMN-endothelial adhesion.

METHODS

Animal Preparation

Ninety adult male Sprague-Dawley (Charles River Lab., Wilmington, MA) weighing approximately 500 g were anesthetized with intraperitoneal ketamine (35 mg/kg). A jugular venous catheter was inserted for fluid or drug infusion (1 ml/h) and hourly intravenous anesthetic dosing (ketamine, 8 mg/kg; xylazine 1 mg/kg). A tracheostomy was performed with a 15-gauge tube. Through this tube, a fine-bore polyester cannula with an external diameter of 0.61 mm and an internal diameter of 0.28 mm was introduced into the anterior segment of the left lung which represented approximately one-third the weight of the left lung. All animals were supine for the duration of the experiment.

Preparation of Solutions

Hydrochloric acid: 0.1 ml 33% HCl (McGaw Park, IL) was mixed with 9 ml of 0.9% NaCl. The final concentration was 0.1 N. When aspirated in a volume of 0.1 ml the mortality rate within 3 hours was less than 10%. A lower concentration of 0.05 N HCl did not lead to neutrophil sequestration or edema of the non-aspirated lung, whereas increased concentrations of greater than 0.2 N or volumes of greater than 0.2 ml increased mortality rates above 30%.

Diethylcarbamazine: (Sigma Chemical Co., St. Louis, MO). After dissolving this lipoxy-

genase inhibitor in 0.9% saline it was administered intravenously (IV) 90 mg/kg as a bolus, 20 minutes prior to aspiration, followed by a 40 mg/kg/h infusion throughout the experiment.

FPL-55712: (Fison Pharmaceuticals, Rochester, NY). A stock solution of this LT receptor antagonist was made up of 2 mg/ml dissolved in 0.9% saline. It was given IV 80 μg/kg as a bolus, 20 minutes prior to aspiration followed by a 40 μg/kg/h infusion throughout the experiment.

OKY 046: The anhydrous crystal of this Tx synthetase inhibitor (ONO Pharmaceuticals, Osaka, Japan) was dissolved in 2 ml of normal saline and 2 mg/kg was administered by IV bolus, starting 30 minutes prior to HCl aspiration and repeated hourly.

SQ 29,548: (Provided as a gift by Dr. M. Ogletree, Squibb Pharmaceuticals, Princeton NJ). This compound has been shown to competitively inhibit Tx receptors as well as the precursor prostaglandin endoperoxide. It is highly selective with only weak antagonistic activity to $PGF_{1\alpha}$ and PGD_2 (8). SQ 29,548 was prepared by dissolving equimolar amounts with tris buffer in 95% ethanol and then evaporating the ethanol under nitrogen. The tris salt of the drug was then dissolved in distilled water. Administration of the drug started 30 minutes prior to HCl aspiration, 2.0 mg/kg as an IV bolus followed by continuous infusion of 0.2 mg/kg/h throughout the experiment. This amount is greater than 10-fold that necessary to blunt the pulmonary pressure response to infusion of a Tx-mimic (endoperoxide analogue) in vivo (9).

Eicosanoid Assays

Plasma concentrations of TxB_2 the stable hydrolysis product of TxA_2 were measured with a double radioimmunoassay (RIA) using an antibody whose cross-reactivity with heterologous prostanoids was less than 1%. Concentrations of LTB_4 in plasma and bronchoalveolar lavage (BAL) fluid were measured in duplicate by radioimmunoassay (rabbit antibody and standards

were obtained from Seragen, Cambridge, MA). Cross-reactivity of the LTB_4 antibody with other LT's, hydroxyeicosatetraenoic acid (HETE), di-HETE, TxB_2, the prostaglandins and their metabolites was less than 1%.

Experimental Protocol

Evans Blue dye 0.2 mg was added to solutions used for aspiration for later confirmation of the site of introduction. Six groups were studied. Five were pretreated with: IV saline (n=18), DEC (n=18), FPL 55712 (n=12), OKY 046 (n=4) or SQ 29,548 (n=4) and then underwent localized aspiration of 0.1 ml 0.1N HCl. The last group (n=18) was pretreated with IV saline and then underwent aspiration with 0.1 ml of 0.9% saline.

The intrabronchial cannula was taken out after aspiration. Three hours later the animal was sacrificed with an overdose of 200 mg ketamine. A thoracotomy was performed and the right and left lung bronchi were clamped in turn. Bronchoalveolar lavage of the left lung, including the aspirated segment and the right lung were then performed in sequence. For each lung, 3 ml of saline was lavaged using the tracheostomy tube. This was repeated three times. The combined lavage return of about 8 ml was introduced into tubes containing 0.3 ml of 0.07M ethylene diamine tetracetic acid. This BAL fluid was centrifuged at 1500 x g for 20 min at 4° and frozen at -20°C and subsequently used for assay of LTB_4 and protein concentration using the spectrophotometric protein dye method (10). The BAL pellet was suspended in 1 ml saline and neutrophils counted after Diff-Quik staining to identify macrophages (AHS del Caribe, Inc., Aguada, Puerto Rico). The results are expressed as polymorphonuclear leukocyte (PMN) x 10^4/ml. Six rats from each experimental group were used for lavage. Another six were used to calculate the wet to dry weight (W/d) ratios of the aspirated and non-aspirated lung segments. This was done after weighing the dyed segment of freshly harvested lung tissue, heating the segment at 90°C to constant weight in a gravity convection oven (Precision Scientific Group, Chi-

cago, IL) for 72 h, and weighing the residuum. Six animals from each group were used for lung histology. After euthanasia the lungs were perfused with 10% formaldehyde and then inflated with the same material to a pressure of 25 cm H_2O. Following fixation, sections from dyed and contralateral segments were taken and stained with hematoxylin and eosin for light microscopic analysis. All microscopic sections were interpreted in a blind fashion by a pulmonary pathologist (LK). Lung sequestration of PMN's was quantitated by counting alveolar septal wall PMN's in the dyed and in the contralateral segment. Only peripheral lung parenchyma was examined. Microscopic fields containing other structures such as airway, large vessels, and pleura were excluded. Leukocyte entrapment was expressed as the mean number of PMN per ten high power fields (x 1000). Animals in which Evans Blue dye appeared in the non-aspirated lung were excluded. In the FPL 55712 group four rats were used for each end point. Finally, other rats (n=16) were used to examine the correlation between PMN sequestration and the increase in W/d of the non-aspirated lung.

Results are presented as mean ± SEM in text, table and figures. Statistical analysis was conducted by least square regression and by a one way analysis of variance. In the latter case if significance was demonstrated, further evaluation was done by a non-paired Student's t-test. Significance was accepted if $p < 0.05$.

Animals in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health, Education and Welfare, Publication No. 78-23 (National Institute of Health), revised, 1978.

RESULTS

Forty minutes after aspiration plasma LTB_4 levels rose to 705 ± 81 pg/ml, higher than saline aspiration values of 220 ± 60 pg/ml ($p < 0.05$). Levels of LTB_4 continued to rise and at three hours there was an increase in LTB_4 in BAL fluid from the aspirated lung and in plasma LTB_4 concentration as well as plasma TxB_2 concentration to values higher than control ($p < 0.05$) (Table 1). The rise in BAL fluid LTB_4 levels were to approximately twice plasma levels ($p < 0.05$) indicating pulmonary synthesis. At this time neutrophils were sequestered in the pulmonary microcirculation 95 ± 8 PMN/10HPF in the aspirated side and 45 ± 3 PMN/10HPF in the non-aspirated side, higher than control values of 8 ± 3 and 5 ± 2 PMN/10HPF (both $p < 0.05$, Fig. 1). The rise in plasma LTB_4 was correlated with neutrophil sequestration in the non-aspirated segment (Fig. 2). There was alveolar diapedesis of neutrophils as measured in BAL fluid of 95 ± 8 PMN/ml, only in the aspirated lung, higher than control values of 3 ± 1 PMN/ml ($p < 0.05$, Fig. 3). This PMN diapedesis was related to BAL fluid LTB_4 concentration (Fig. 4).

Localized aspiration induced an increase in protein concentration in BAL of 4520 ± 300 μg/ml and 2320 ± 120 μg/ml in the aspirated and non-aspirated lungs respectively, higher than control values of 480 ± 60 μg/ml and 410 ± 120 μg/ml (both $p < 0.05$, Fig. 5). The permeability was associated with an increase in lung W/d of 6.5 ± 0.2 and 5.3 ± 0.1, higher than following saline aspiration 3.4 ± 0.1 and 3.3 ± 0.2 (both $p < 0.05$, Fig. 6). Pretreatment of rats with the lipoxygenase inhibitor DEC prevented the aspiration induced rise in plasma and BAL LTB_4 as well as plasma TxB_2 ($p < 0.05$)(Table 1). Aspiration injury was reduced : leukosequestration in the aspirated lung was 58 ± 6 and in the non-aspirated side 28 ± 3 PMN/10HPF; BAL neutrophil accumulations were 44 ± 6 PMN/ml; BAL protein concentration 2120 ± 50 μg/ml, 1240 ± 150 μg/ml; and the W/d weight ratio 5.0 ± 0.2, 3.6 ± 0.1 (all $p < 0.05$). A significant correlation was found between the number of PMN sequestered in lung and the degree of lung weight gain (Fig.

7)

Other rats were pretreated with the LT receptor antagonist, FPL 55712. They demonstrated a rise in plasma LTB_4 and TxB_2, but this agent was otherwise as effective as DEC in preventing aspiration injury (Figs. 1,3,5,6,7).

Finally, in order to examine the hypothesis that Tx may enhance LTB_4 synthesis, animals were pretreated with Tx synthesis and receptor antagonists. Three hours after aspiration the generation of LTB_4 was significantly reduced ($p < 0.05$) (Table 1).

DISCUSSION

The aim of this study was first to define the role of LTB_4 in aspiration induced neutrophil adhesion and edema. The data provide evidence of a causal relationship. Thus, following acid aspiration there was generation of LTB_4 in plasma and lung (Table 1); secondly, a significant correlation was found between plasma LTB_4 levels and remote pulmonary neutrophil sequestration (Fig. 2); thirdly, leukotriene inhibitors minimized this event as well as diapedesis into the aspirated segment (Fig. 1,3,4); fourthly, neutrophil sequestration determined lung edema (Fig. 7); and finally, the inhibition of LT synthesis or receptors limited lung leukosequestration and permeability edema (Figs. 5-7).

The second aim of the study was to examine the relationship of LTB_4 and TxA_2 in determining aspiration injury. In previous studies we have found that plasma TxB_2 generation was correlated with neutrophil adhesion (11). Further, inhibition of Tx synthesis or Tx receptors prior to acid aspiration reduced neutrophil sequestration in both aspirated and non-aspirated regions. These observations along with present results provide substantial data which indicate that LTB_4 and TxA_2 interact in a synergistic fashion to promote PMN adhesion: first, inhibition of Tx synthesis with OKY 046 or Tx receptors with SQ 29,548, significantly reduced LTB_4 synthesis (Table 1). The reverse was also true where lipoxygenase inhibition prevented Tx synthesis; secondly, Tx mimic-stimulated PMN adhesion to an endothelial monolayer was prevented by FPL 55712 (3); thirdly, Tx mimic when placed in abraded skin chambers led to LTB_4 synthesis and PMN diapedesis. Inhibition of LTB_4 synthesis with DEC abolished this event; fourthly, LTB_4 induced PMN diapedesis was limited with OKY 046 (6). Taken together these data confirm our hypothesis that LTB_4 and Tx are obligate co-factors in regulating PMN-endothelial interactions.

The interaction between these two eicosanoids in determining PMN adhesion and

diapedesis has been shown in another setting, using the skin dermabrasion chamber as the assay for diapedesis. Thus, ischemic plasma which contains high concentrations of TxB_2 and LTB_4 induces neutrophil diapedesis. This event can be prevented by a Tx synthetase inhibitor as well as by LT antagonists (12). Further, during diapedesis there is de novo synthesis of both eicosanoids as assaye ! by rising levels in the blister fluid (12). This eicosanoid synthesis was essential for PMN accumulations.

The mechanism whereby LTB_4 and TxA_2 moderate PMN-endothelial interactions following aspiration is not clear. Although both agents are involved in determining neutrophil accumulations in the aspirated and non-aspirated lung regions, additional mediator(s) must be operative. Thus, it has been reported that in the aspirated region, PMN accumulations are CD 18 independent (13). This is not the case in the non-aspirated regions. It is possible that at the site of aspiration LTB_4 and TxA_2 mediate the synthesis of cytokines which later activate local endothelial cells to increase PMN adhesion in a non CD 18 dependent fashion. The 3 to 4 hours delay in the occurrence of adhesion and diapedesis is in accord with cytokine-induction of endothelial adhesion protein expression. In further support of this thesis, tumor necrosis factor antiserum limited neutrophil accumulation in the aspirated site. Further, a protein synthesis inhibitor, to prevent upregulation of adhesion proteins by the endothelium, minimized the delayed PMN-endothelial interaction in the aspirated region (14). These data provide evidence that a non-CD 18 dependent endothelial adhesion receptor mediates PMN accumulations in the aspirated lung segment. We postulate that the two eicosanoids, particularly LTB_4 may induce TNF synthesis in the lung that in turn will activate endothelial cells to express the endothelial leukocyte adhesion molecule-1 (ELAM-1) (15,16), an adhesion protein which is CD 18 independent.

Neutrophil sequestration in the non-aspirated lung is shown by present data to be related to plasma LTB_4 (Fig. 2). Entrapment of PMN in the non-aspirated lung has been demonstrated to

be limited by pretreatment with an anti CD 18 mAb (submitted for publication). LTB_4 directly activates PMN CD 18 adhesion receptors (7). In low LTB_4 concentrations 10^{-9}M there is a rapid change in configuration of CD 18 associated with increased adhesion. In higher concentrations there is upregulation of these receptors. Tx-mimic may also activate PMN CD 18 receptors and promote PMN-endothelial adhesion, an event prevented with a leukotriene receptor antagonist (3).

Based on these and other data we hypothesize that the sequence of events following acid aspiration is: first, within 30 minutes platelets are activated to release Tx (1); secondly, that this rise in plasma TxA_2 in turn activates PMN to release LTB_4 ; thirdly, both agents act as autocoids and induce further eicosanoid synthesis. These eicosanoids activate both neutrophil adhesion receptors as well as neutrophil oxidative metabolism, perhaps a prerequisite for lipoxygenation and LTB_4 generation. Thus, Tx inhibitors prevent intracellular production of H_2O_2 by circulating neutrophils (17) as well as limit their LTB_4 production (Table 1). Both eicosanoids likely activate neutrophil CD 18 adhesion receptors. Finally, by stimulating cytokine synthesis they may lead to CD 18 independent or dependent PMN adhesion in the aspirated or non-aspirated lung respectively.

Neutrophil adhesion to the microcirculation of the non-aspirated lung is a prerequisite for permeability increase in this setting. Thus, neutrophil depletion or inhibition of their remote adhesion using an anti-CD 18 mAb, limits the subsequent pulmonary microvascular leak (17). Present data confirm that neutrophil adhesion to the microvasculature is associated with barrier dysfunction. This is evidenced by the accumulation of increased protein in BAL fluid and the correlation of sequestered neutrophils with the W/d weight ratio of the lungs (Fig. 7). Finally, it is believed that the process of adhesion is a prerequisite for PMN to release H_2O_2 and granular contents (18). Adhesion provides a micro-environment where high concentrations of these vaso-

toxic agents can act on the microcirculation (19).

In summary, taken together data suggest that LTB_4 and Tx are co-factors in mediating acid aspiration injury. These eicosanoids activate neutrophils and promote their adhesion in the microvasculature a requisite for permeability edema.

Figure 1. Localized aspiration induced generalized lung leukosequestration. Pretreatment with either a lipoxygenase inhibitor or LT receptor antagonist attenuated this event. The symbols * and † indicate $p < 0.05$ relative to control and saline-HCl group respectively.

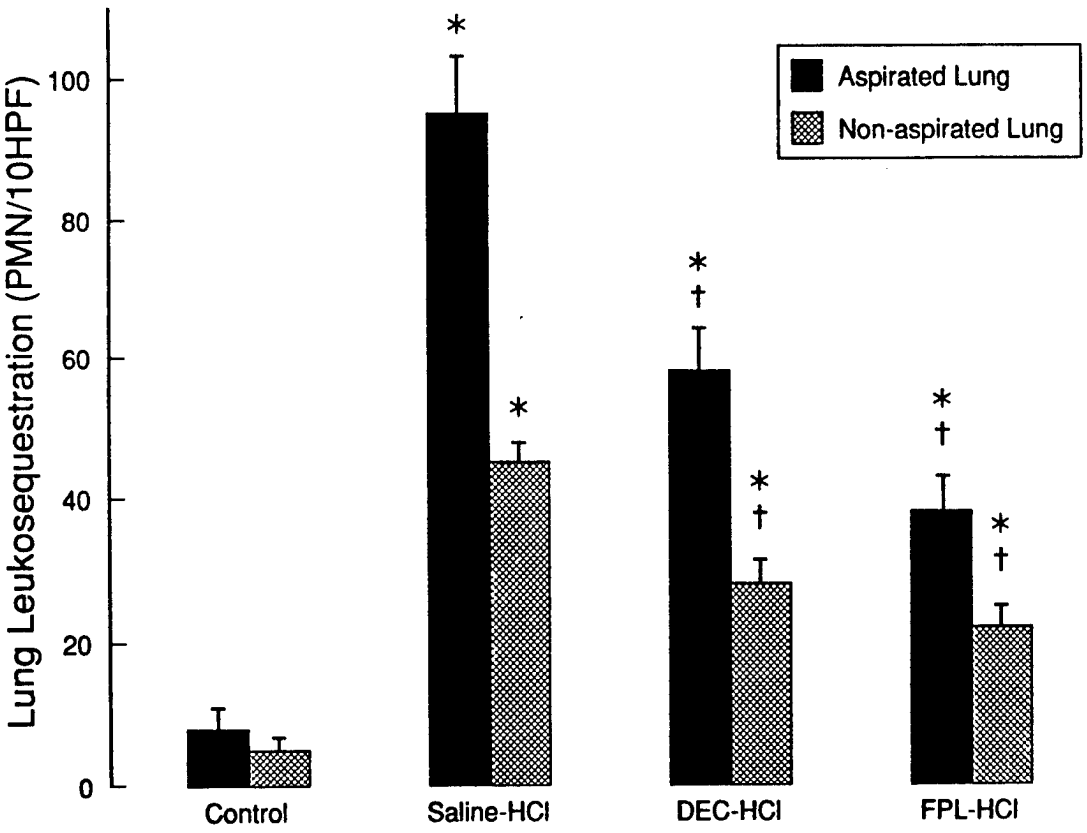

Figure 2. A significant correlation ($r=0.83$, $p < 0.05$) was found between plasma LTB_4 levels and PMN sequestration in the non-aspirated lung. Treatment with DEC reduced leukosequestration.

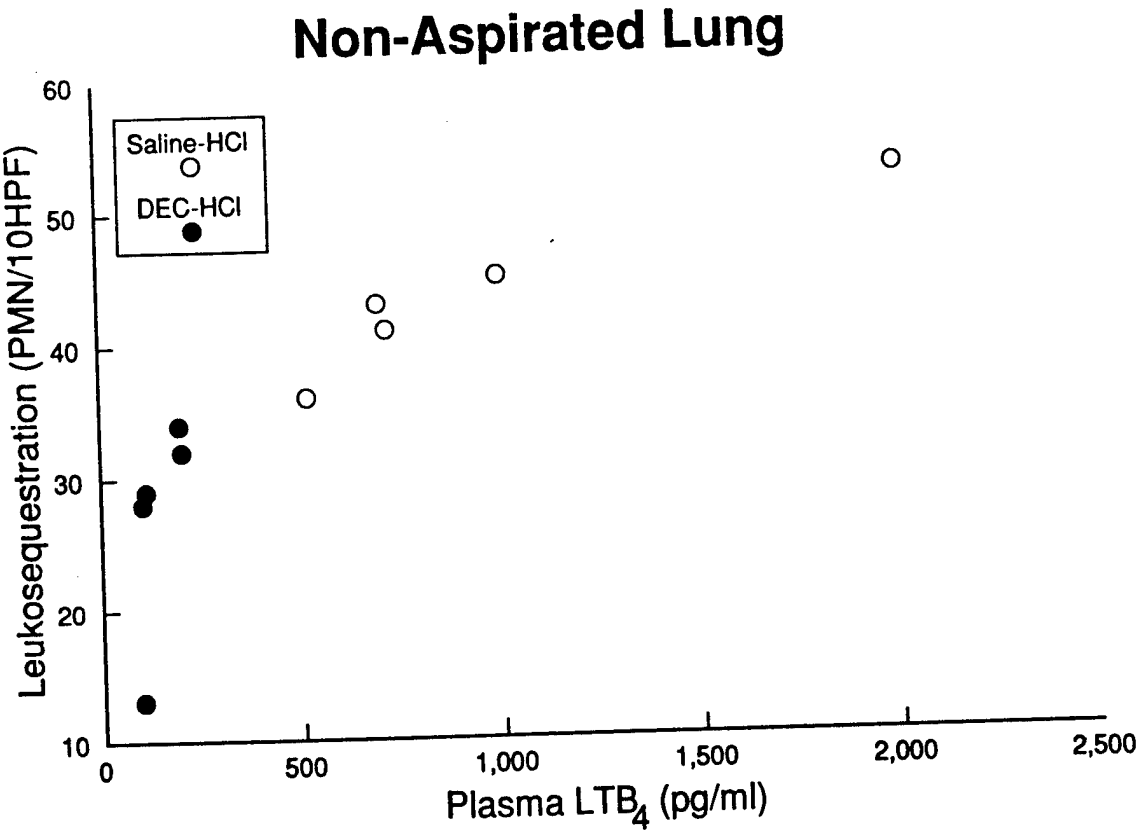

Figure 3. Acid aspiration induced neutrophil diapedesis only in the aspirated side. LT inhibitors limited this event. The symbols * and † indicate $p < 0.05$ relative to control and saline-HCl group respectively.

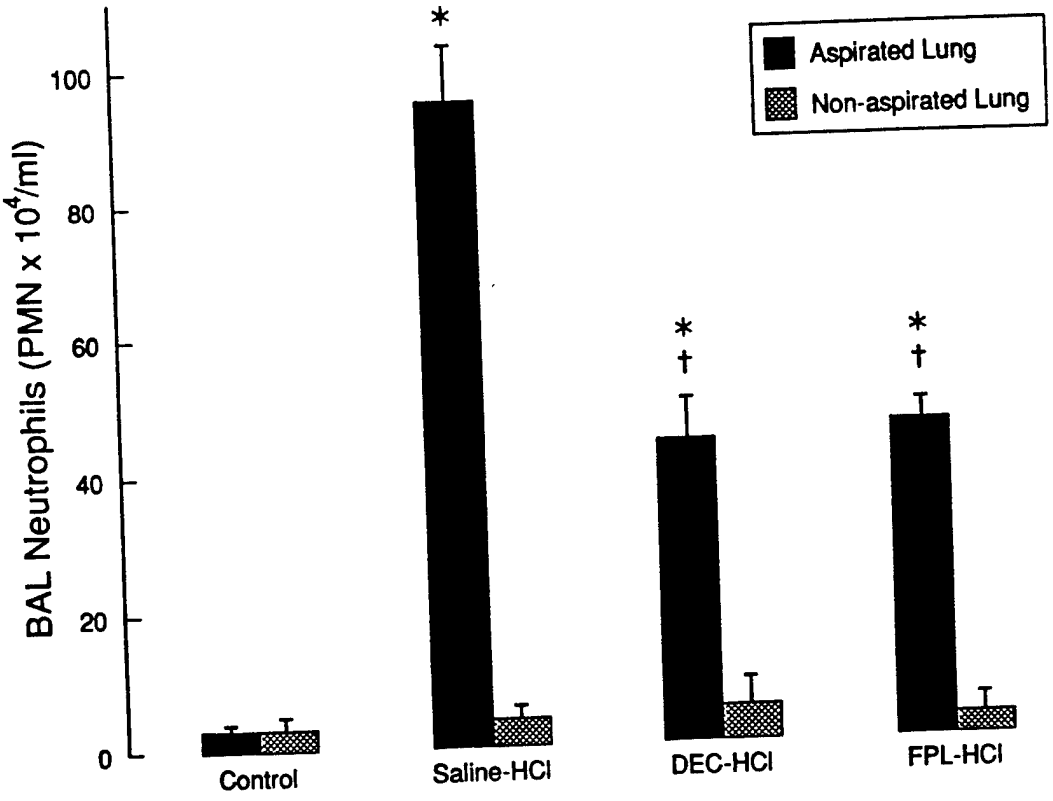

Figure 4. Neutrophil accumulations in BAL were correlated ($p < 0.05$) with LTB_4 concentration in this fluid 3 hours following acid aspiration.

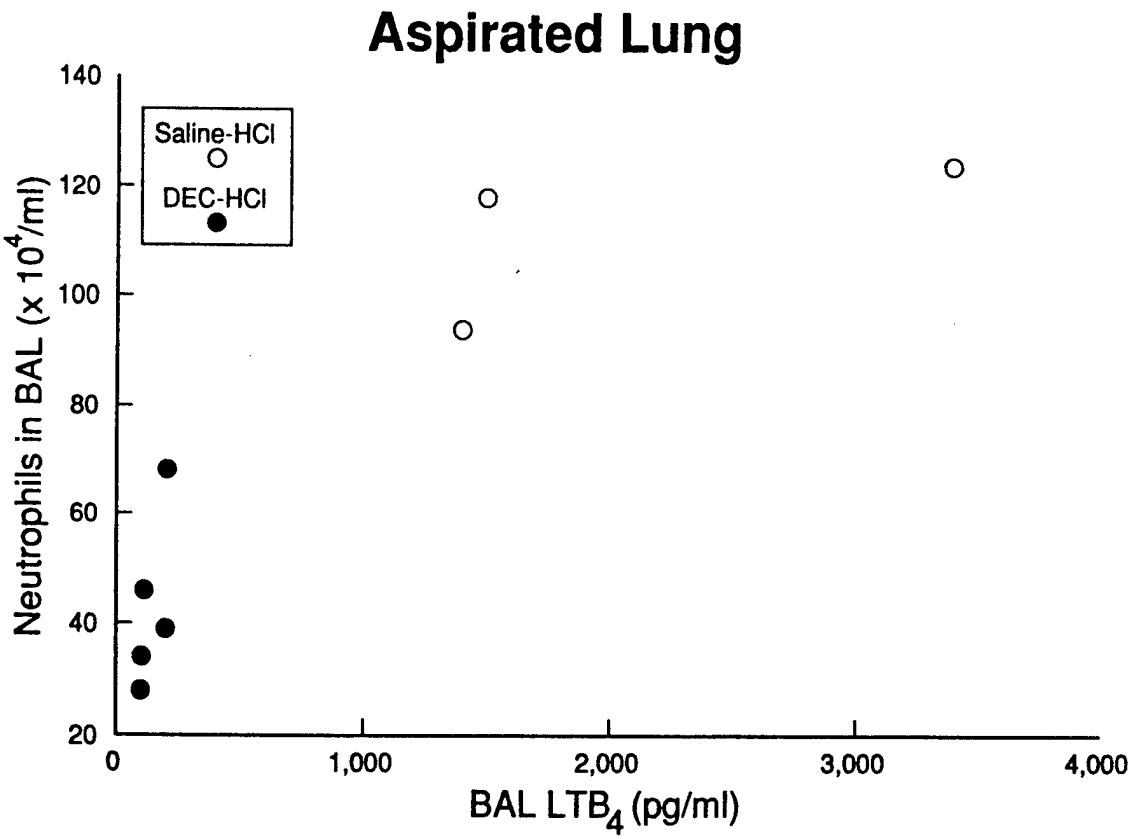

Figure 5. LT inhibitors reduced aspiration induced protein leak in BAL. The symbols * and † indicate $p < 0.05$ relative to control and saline-HCl group respectively.

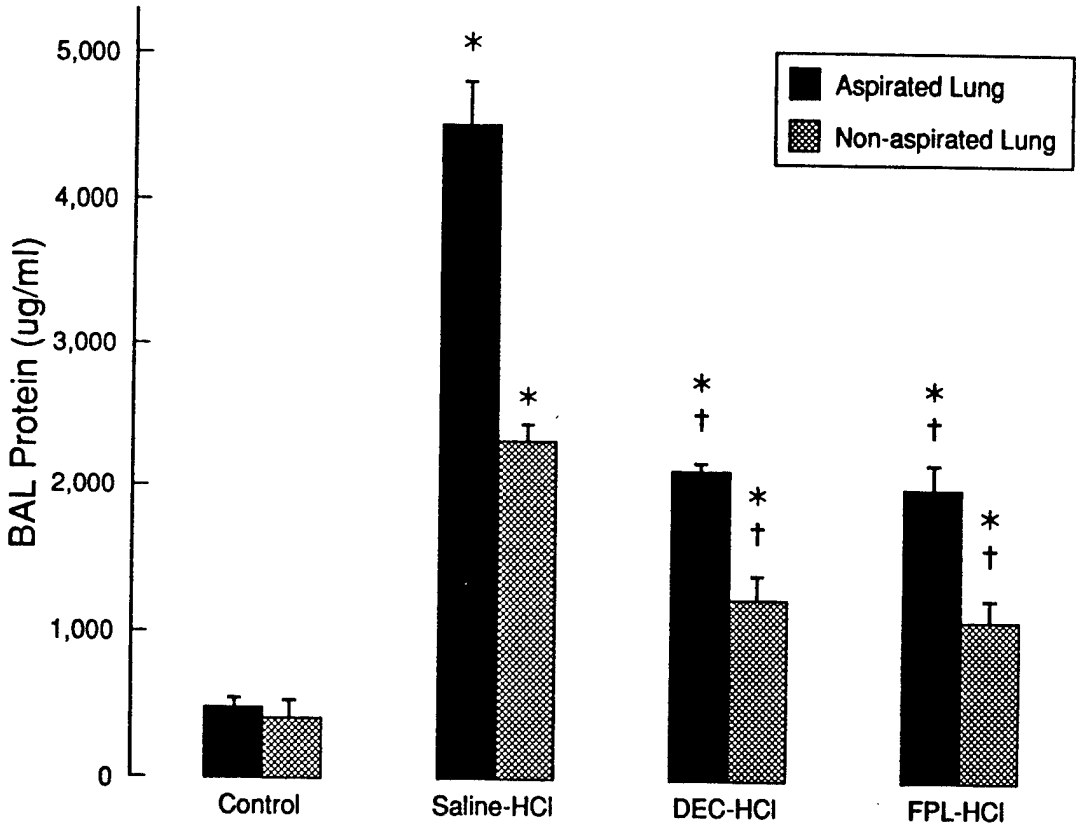

Figure 6. Localized aspiration induced generalized lung edema. Inhibition of lipoxygenase or LT receptors attenuated this event. The symbols * and † indicate $p < 0.05$ relative to control and saline-HCl group respectively.

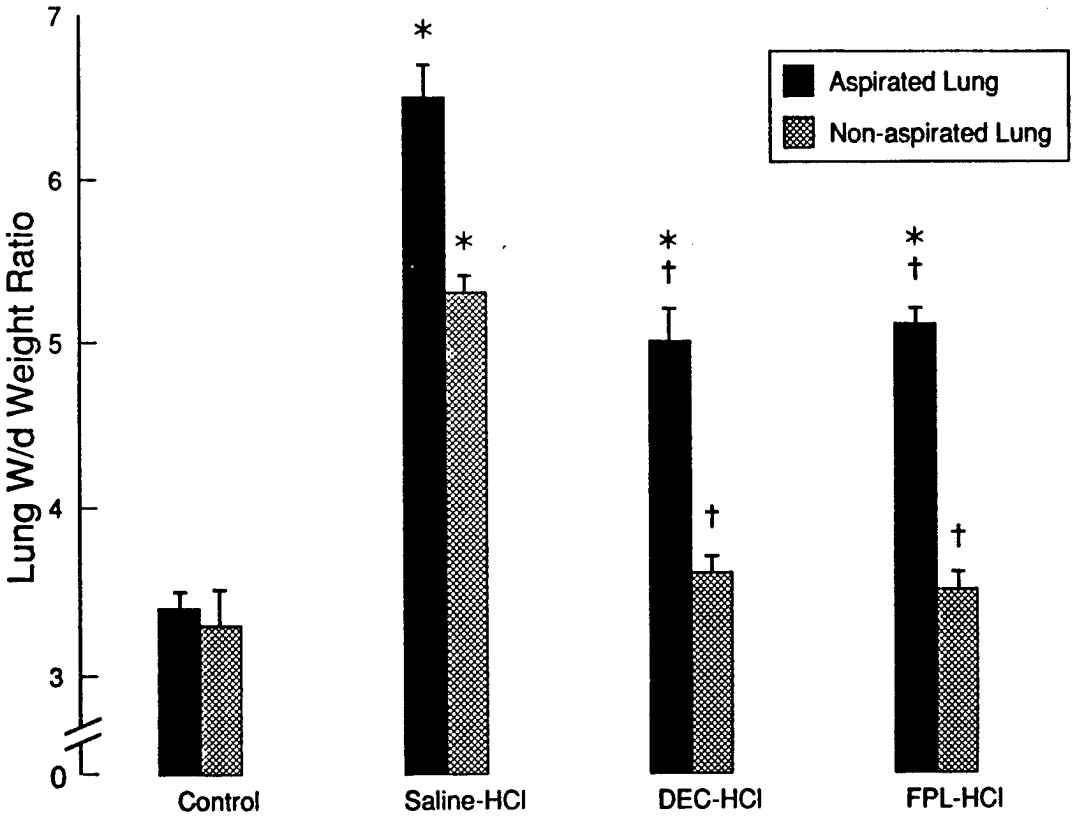

Figure 7. Neutrophil sequestration in the non-aspirated lung of the saline-HCl group was correlated with the W/d weight ratio (r=0.88). Use of LT antagonists limited PMN sequestration and lung weight gain.

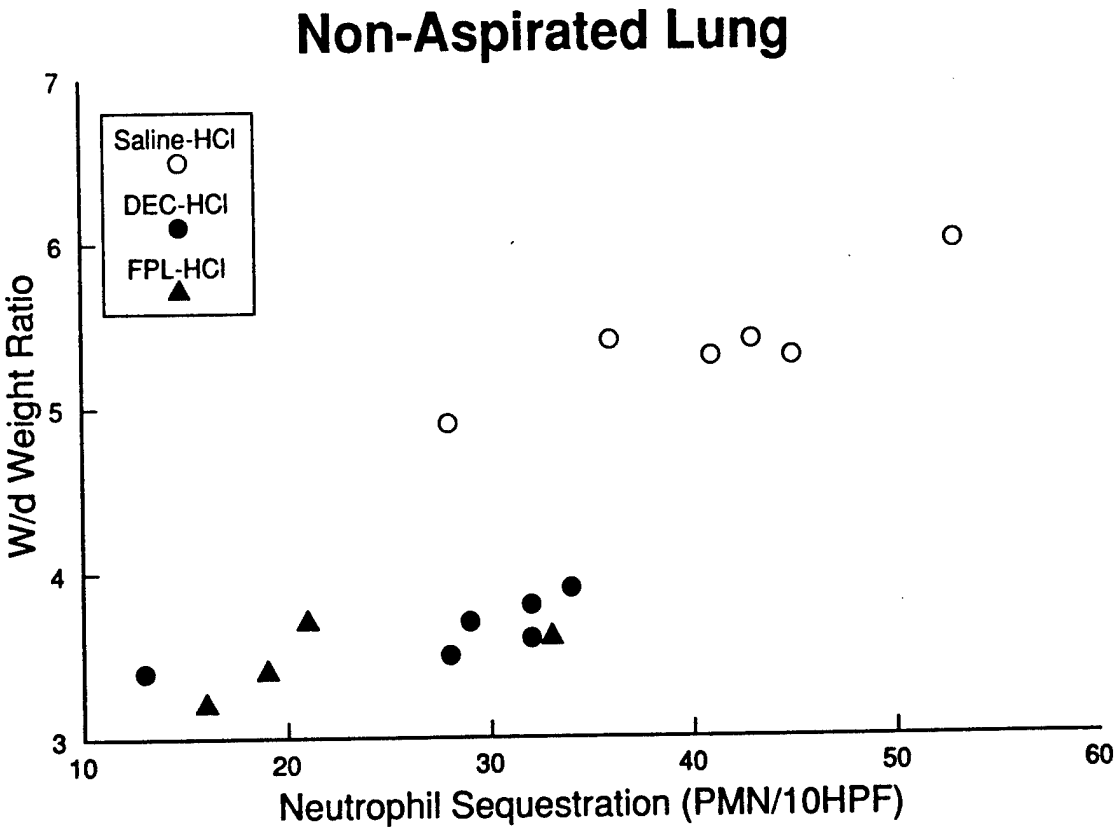

TABLE 1

EICOSANOID LEVELS 3 HOURS FOLLOWING ASPIRATION‡

	LTB_4		TxB_2
	Plasma	**BAL of aspirated lung**	**Plasma**
Control	218 ± 30	281 ± 68	460 ± 45
HCl-Saline	988 ± 264*	1766 ± 317*	1870 ± 215*
HCl-DEC	144 ± 23 * †	136 ± 35 * †	338 ± 61†
HCl-FPL55712	996 ± 118*	---	1650 ± 80*
HCl-OKY 046	500 ± 60 * †	---	450 ± 194 †
HCL-SQ29,548	358 ± 13 * †	---	1328 ± 141 *†

‡ Data are pg/ml.

The symbols * and † indicate $p < 0.05$ relative to saline (control) and HCl-saline respectively.

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